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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/598,482

02/06/2007

Philip Wilson Howard

065435-9081-US00

6002

23510 7590 05/22/2008  
MICHAEL BEST & FRIEDRICH LLP  
ONE SOUTH PINCKNEY STREET  
P O BOX 1806  
MADISON, WI 53701

EXAMINER

KIFLE, BRUCK

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

05/22/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/598,482	<b>Applicant(s)</b> HOWARD ET AL.	
	<b>Examiner</b> Bruck Kifle	<b>Art Unit</b> 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 February 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-21, 23 and 25-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-21, 23 and 25-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/2006, 01/2007</u> .  | 6) <input type="checkbox"/> Other: _____                          |

***Claim Rejections - 35 USC § 112***

Claims 1-21, 23 and 25-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) In claim 1 the phrase “and salts, solvates, chemically protected forms thereof” should be rewritten as, for example, “or a pharmaceutically acceptable salt thereof” to comply with proper Markush language and limit the salt to a pharmaceutically acceptable salt as this appears to be the intended use of these compounds. See below rejections for “solvates” and “chemically protected forms.”

ii) The definition of the “chemically protected forms” is unclear. Are these additional protections beyond what has been recited in the claims? It is unclear what these compounds look like and what they are being protected against.

iii) The phrase “optionally substituted” without saying which substituents are intended is indefinite. One skilled in the art cannot say which substituents are permitted and which ones are not.

iv) The groups C<sub>3-20</sub> heterocyclyl and C<sub>5-20</sub> aryl are indefinite because it is not known how many heteroatoms are present, what kinds of heteroatoms are involved, what size ring is intended and how many rings are present. A heterocyclyl necessarily requires the presence of a hetero atom and cannot be made up of only carbon atoms. The lowest number of carbon atoms permitted in an aryl is 6. It is unclear what is intended by a C<sub>5</sub> aryl.

v) It is unclear how “X” can be other than O in claims 8-21. The process of making the compounds of formula IIIa and IIIb do not permit X to be S or NH.

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vi) Claims 26 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The reaction steps.

vii) Regarding claim 8, the phrase "e.g." renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 1-21, 23 and 25-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical salt, does not reasonably provide enablement for solvates of the compound of formula Ia and Ib. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Applicants have not shown how one skilled in the art can arrive at a given solvate. None of the compounds made are crystallized out as solvates. Arriving at a given solvate is not routine experimentation because it is unpredictable. One cannot make any solvate of a compound.

Solvates are different chemical entities, they are not just impurities included in a compound. Pharmaceutically acceptable salts are additions and therefore not the same. Additions are obvious variation "after" the compounds are obtained, thus, can be allowed with the compounds. Solvates or hydrates must be obtained at the time the invention was made. If Applicants do not have the solvates or hydrates at the time the invention was made, they are not in possession of them because they are unpredictable.

Claim 25 is drawn to the treatment of a proliferative disease. The specification does not provide enablement for the treatment of a proliferative disease generally. No compound has ever been found that can treat proliferative diseases generally even though massive efforts have been directed towards this end. Since this assertion is contrary to what is known in oncology, proof must be provided that this revolutionary assertion has merits. Nearly all anticancer drugs are effective against only a limited group of related cancers. Therefore, a compound effective against a proliferative disease generally would be a revolutionary exception. Applicant is asserting that he succeeded where others have failed. Where extensive efforts have all failed, it is reasonable for the Patent and Trademark Office to require proof that the claimed invention actually works for this specific utility. It is well established that a utility rejection is proper when scope of enablement is not reasonably correlated to the scope of the claims. (In re Vaeck 20 USPQ2d 1439, 1444, In re Ferens 163 USPQ 609).

In re Buting 163 USPQ 689 establishes that even clinical tests showing that a compound found to be useful in the treatment of two types of cancers was not sufficient for a much broader range.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

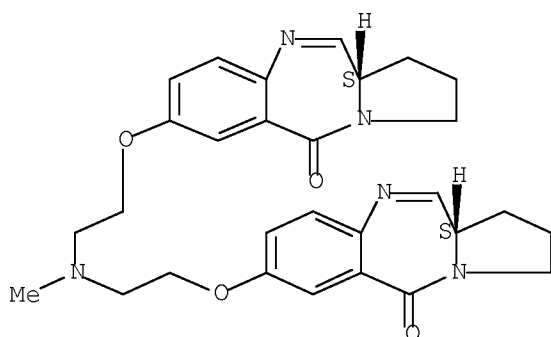
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 8, 10 and 18-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Farmer et al. (Tetrahedron Letters (1988), 29(40), 5105-8). The claims read on the following two compounds (see Abstract).

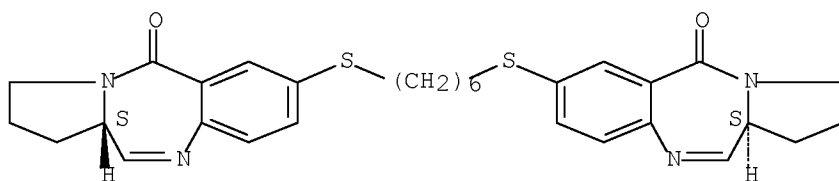
RN 123064-64-2 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-ethanediylloxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 123064-63-1 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,6-hexanediylbis(thio)]bis[1,2,3,11a-tetrahydro-, [S-(R\*,R\*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Claims 8-11 and 18-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Bose et al. (Journal of the Chemical Society, Chemical Communications (1992), (20), 1518-20). The claims read on the compounds of formula 8 (see page 1519).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8, 9, 11-16 and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smellie et al. (Biochemistry (2003), 42(27), 8232-8239). The reference teaches the compound of formula 2d (see page 8232). The claims differ by requiring a C<sub>8</sub> linker between the PBD moieties over the prior art C<sub>6</sub> linker. It has been long established that structural relationship varying the size of a linking carbon chain - is per se obvious. Specifically, In re Shetty, 195 USPQ 753, In re Wilder, 195 USPQ 426 and Ex Parte Greshem 121 USPQ 422 all feature a compound with a C<sub>2</sub> link rejected over a compound with a C<sub>1</sub> link. Similarly, In re Chupp, 2 USPQ 2nd 1437 and In re Coes, 81 USPQ 369 have a C<sub>1</sub> link unpatentable over a C<sub>2</sub> link. Ex parte Ruddy 121 USPQ 427 has a C<sub>3</sub> link unpatentable over a C<sub>1</sub> link. Ex parte Nathan, 121 USPQ 349 found the insertion of a C<sub>2</sub>H<sub>4</sub> link obvious. In all of these cases, the variation was per se obvious and did not require a specific teaching.

Copious amount of prior art was found but only exemplary references have been used in the rejections in the instant office action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle whose telephone number is 571-272-0668. The examiner can normally be reached on Mondays-Fridays from 8:30 AM -6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bruck Kifle/  
Primary Examiner  
Art Unit 1624

BK  
May 20, 2008